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Review

GLUT1 deficiency syndrome 2013: Current state of the art

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ABSTRACT

Glucose transporter type 1 deficiency syndrome (GLUT1DS) is the result of impaired glucose transport into the brain. The "classic" GLUT1DS patient presents with infantile seizures (resistant to traditional seizure medications), developmental delay, acquired microcephaly, hypotonia, spasticity, and a complex movement disorder consisting of ataxia and dystonia. However, over the years, other clinical manifestations have been described, such as paroxysmal exertion-induced dystonia with or without seizures, choreoathetosis, alternating hemiplegia, and other paroxysmal events, such as intermittent ataxia, dystonia, and migraine.

At the current state of the art in understanding of GLUT1DS, classifying the disease phenotype as "classical" or "non-classical" seems to be of limited clinical utility. It seems more appropriate to think in terms of a broad clinical spectrum in which we can observe intellectual impairment, acquired microcephaly, epilepsy, and movement disorders characterized by different clinical manifestations and degrees of severity.

Lumbar puncture, a simple investigation, should be considered the first diagnostic step that, moreover, is feasible worldwide. Thereafter, mutational analysis of the solute carrier family 2 (facilitated glucose transporter) member 1 (SLC2A1) gene should be performed in patients with highly suggestive clinical findings and low cerebrospinal fluid glucose (<50 mg/dl or ratio <0.60).

Early diagnosis is critical because it allows prompt initiation of treatment with a ketogenic diet (KD). Childhood is the critical period for treatment of GLUT1DS: early diagnosis is crucial for an effective etiological therapy. KD treatment can be useful in adulthood too. Compliance has been found to be much better in GLUT1DS than in the other conditions for which KD treatment is indicated.

1. Introduction

Glucose is the essential substrate for brain energy metabolism. In the resting state, the adult brain can consume up to 25% of the body's total glucose supply,[1] while in infants and children it can use as much as 80%.[2]

The diffusion of this essential fuel across the blood–brain barrier is facilitated by glucose transporter type 1 (GLUT1). In the brain, GLUT1 interacts with other specific GLUT isoforms mediating glucose transport into astrocytes and neurons.[3]

GLUT1 deficiency syndrome (GLUT1DS) results from impaired glucose transport into the brain.[4]

The classic GLUT1DS patient presents with infantile seizures (often resistant to traditional seizure medications), developmental delay, acquired microcephaly, hypotonia, spasticity, and a complex movement disorder consisting of ataxia and dystonia.[5]

Recently the clinical spectrum of GLUT1DS has been broadened to include developmental delay, epilepsy and/or movement disorders,[6] as well as familial and sporadic paroxysmal exercise-induced dyskinesia with or without epilepsy.[7] There are also varying degrees of cognitive impairment associated with dysarthria, dysfluency, and expressive language deficits. In most patients, the cerebrospinal fluid (CSF)-to-blood glucose ratio is below 0.50, and CSF lactate is low to normal.

A diagnosis of GLUT1DS can be confirmed by molecular analysis of the solute carrier family 2 (facilitated glucose transporter) member 1 (SLC2A1) gene, while analysis of glucose uptake into erythrocytes can confirm the impaired GLUT1 function. Early diagnosis is critical because it allows prompt initiation of treatment with a ketogenic diet (KD), which is a high-fat, low-carbohydrate diet that mimics the metabolic state of fasting. Since ketones use another transporter to enter the central nervous system, they can provide the brain with an alternative source of fuel, thereby effectively correcting the impaired brain energy metabolism[8] and reducing the frequency of the seizures and the severity of the dystonic movement disorder.

The normal rate of cerebral oxygen consumption is low during the fetal and perinatal periods; it then increases in a linear fashion

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to peak at the age 3 of years, thereafter remaining high until adolescence when it shows a gradual decline.[9] Therefore, childhood is the critical period for treatment of GLUT1DS: early diagnosis is crucial for effective KD treatment.

2. Molecular basis

GLUT1 is a member of the GLUT family of facilitative glucose transporters, which comprises 13 proteins (gene symbol SLC2A, protein symbol GLUT). Cloned and sequenced in 1985, GLUT1/SLC2A1 (OMIM 138140) was the first gene of this family to be identified.[10] Located on the short arm of chromosome 1 (1p34.2), this gene is 35 kb long and consists of 10 exons.

GLUT1 is constitutively expressed in most tissues and selectively expressed in erythrocytes, brain microvessels and astroglia.[3] It exists in two molecular weight forms (45 and 55 kDa), which differ only in the extent of glycosylation of the protein.[11] The 45 kDa form is detected in most cells including astrocytes and may be responsible for basal glucose uptake by cells. The 55 kDa form is found predominantly in the endothelial cells of brain microvessels and erythrocytes, where it is the principal glucose transporter.[6] If there is a deficiency of GLUT1, the quantity of glucose passing from the blood into the brain can be reduced, and this causes a dysfunction in the central nervous system.

Human and animal data suggest that there is only a narrow safety margin for glucose transport across the blood–brain barrier to meet the needs of brain metabolism and cerebral function. A milder clinical phenotype with intermittent symptoms (epilepsy, dyskinesias, ataxia) may be predicted in the presence of a 25–35% reduction in GLUT1 transporter function,[12] while a more severe phenotype is likely to result from reductions in the order of 40–75%.[13]

Most detected SCL2A1 mutations are de novo; in familial cases the condition is inherited as an autosomal dominant trait with complete penetrance. A case of autosomal recessive transmission has also recently been described.[14] All detected mutations are heterozygous; indeed, homozygous GLUT1 mutations are presumably lethal in utero.[15]

Patients with missense mutations generally present with moderate to mild symptoms, but no clear-cut phenotype–genotype correlations have been established. Indeed, patients sharing identical mutations often do not have identical clinical manifestations, which suggests that there are additional mechanisms at work, such as disease-modifying genes and proteins that alter phenotype and potentially contribute to the pathophysiology of this complex entity.[16] Leen et al.[8] studied 57 patients, trying to identify a specific relationship between genotype and phenotype. They found that mild mental retardation was more often present in patients with a missense mutation (Type A), and movement disorders than in those with translation initiation mutations (Type B) or multiple exon deletions (Type C). However, severe mental retardation was found to be present in a few Type A patients and mild mental retardation in some Type B or C patients. Additionally, patients with the same mutation displayed phenotypic heterogeneity, in terms of range of clinical expression and severity. It is possible that other secondary genes or other proteins are involved in glucose transport, which might explain the phenotypic diversity of this disease.[17]

GLUT1 deficiency syndrome may also occur as a part of broader genetic syndromes, as seen in microdeletion syndromes involving the SLC2A1 gene.[18]

3. Clinical phenotypes

3.1. Classical phenotype

GLUT1 deficiency syndrome was first described in 1991 as an early-onset childhood epileptic encephalopathy.[19] This phenotype, now defined "classical", was rapidly expanded to include epileptic encephalopathy with different seizure types, developmental delay, acquired microcephaly, complex movement disorders (variable combinations of ataxia, dystonia and spasticity), and paroxysmal events. Seizures were initially described as brief, subtle myoclonic limb jerking with alternating staring and eye-rolling, unresponsiveness, hypotonia and head bobbing. Now, also generalized seizures of all types (absences, generalized tonic-clonic, myoclonic, atonic, etc.) are considered features of the classical phenotype. The movement disorders presented differ from patient to patient, but most frequently consist of ataxia and spasticity. Paroxysmal events of possibly non-epileptic origin include intermittent ataxia, periodic confusion, periodic weakness, periodic limb paralysis, recurrent headaches, and intermittent sleep disturbances.

The clinical severity of the classical phenotype varies, ranging from mild motor and cognitive dysfunction between epileptic attacks to severe neurological disability, with some patients never achieving the ability to speak or walk unsupported.[6] In most patients with the classical phenotype neurological symptoms are not influenced by fasting or food intake,[20] even though there are isolated reports of paroxysmal worsening of symptoms (mainly movement disorders) with prolonged fasting.[8]

3.2. Non-classical phenotypes

Several clinical variants of GLUT1DS have been reported over the two decades since the first description of the classical phenotype. Brockmann's classification is the one most cited in the literature,[6] and it classifies patients into the following groups on the basis of their symptoms: (i) carbohydrate-responsive symptoms, characterized by a correlation between fasting and neurological deterioration including seizure frequency; (ii) predominant ataxia or dystonia, but without seizures, and (iii) paroxysmal exertion-induced dyskinesia and seizures.

However, over the years numerous atypical clinical manifestations have been described, such as paroxysmal exertion-induced dystonia (PED) with[21] or without seizures,[7,22,23] choreoathetosis,[24] alternating hemiplegia[25] and other paroxysmal events,[26] such as intermittent ataxia, dystonia, and migraine.

At the current state of the art in understanding of GLUT1DS, classifying the disease phenotype as "classical" or "non-classical" seems to be of limited clinical utility. It seems more appropriate to think in terms of a broad clinical spectrum in which we can observe:

3.2.1. Intellectual impairment

Intellectual impairment in patients with GLUT1DS varies widely and may include: language delay, expressive language difficulties possibly associated with dysarthria, learning difficulties, and mild, moderate or severe cognitive delay, but without a significant neuropsychological profile. In our experience, cognitive impairment is often proportional to the severity of other symptoms; indeed intelligence quotient (IQ) is usually normal in patients with minimal symptoms.

Leen et al., in their sample[8] of 57 patients, found mental retardation (from mild to severe) in almost all the patients with a severe phenotype (46 out of 48), in half of those with a mild phenotype (4 out of 8), and in neither of the two patients with minimal symptoms.

Other psychiatric symptoms, such as behavioral difficulties, depression, and attention deficit hyperactivity disorder, are only sporadically described.[28]

3.2.2. Acquired microcephaly

This is a frequent but not essential component of the clinical spectrum.

Acquired microcephaly was mainly observed in classical phenotype patients.[28] Adult cases with "minimal symptoms" do not present microcephaly, whereas it can be found in around 40% of patients with mild phenotypes and in around 50% of those with a severe phenotype (classical De Vivo syndrome).[8]

3.2.3. Epilepsy

GLUT1 deficiency syndrome should be considered in the differential diagnosis of any form of intractable epilepsy.[29] Patients usually develop seizures in infancy and early childhood.

In infants, seizures are described as brief, subtle myoclonic limb jerks with alternating staring and eye-rolling, sudden-onset pallor, a dazed expression, horizontal roving eye movements, unresponsiveness, hypotonia and head bobbing. The EEG usually shows multifocal spike discharges.

Pong et al.[30] recently reviewed 87 patients with GLUT1DS and noticed that 78 (90%) had epilepsy with a mean age at onset of 8 months. Seizures were a mixture of different types: generalized tonic-clonic (53%), absence (49%), complex partial (37%), myoclonic (27%), drop (26%), tonic (12%), simple partial (3%), and spasms (3%) (these authors described the first two cases of spasms in GLUT1DS).

In childhood, seizures are frequently myoclonic and generalized;[28] myoclonic astatic epilepsy (MAE) is a commonly reported form.[31,32] This finding could be linked to brain maturation; indeed, as the brain matures, seizures become synchronized and manifest clinically as generalized events associated with 3–4 Hz spike-and-wave discharges.

Some authors have described forms of epilepsy that are particularly responsive to carbohydrate intake.[6]

However, it is important to stress that forms described as MAE and caused by SLC2A1 mutations cannot be considered "typical": GLUT1DS was present in only four out of 84 MAE probands (5%) investigated by Mullen et al.[31] and it is important to underline that two of these patients also presented PED in childhood; another presented ataxia, dysarthric speech and deceleration of head growth.

Idiopathic generalized epilepsies (IGEs), not usually drug-responsive, have also previously been described. More than 10% of early-onset[33,34] or myoclonic[35] absence epilepsies are caused by mutations of the SLC2A1 gene.

Recently, a very interesting article by Arsov et al.[36] showed that mutations of SLC2A1 are responsible for approximately 1% of all IGEs. The authors analyzed a total of 504 probands with IGEs (juvenile myoclonic epilepsy – 32%, juvenile absence epilepsy – 21%, childhood absence epilepsy – 31%, generalized tonic-clonic seizures – 13%, and unspecified forms of IGE – 2%) and 470 controls. In total, seven of the 504 probands and none of the 470 controls had mutations demonstrating a functional effect on the protein product. The cases described had a history of IGEs, with seizures responding well to antiepileptic drugs (AEDs), and normal intellectual outcome, although closer analysis of the patients' clinical records revealed cases with atypical forms of juvenile myoclonic epilepsy who became seizure-free on oxcarbazepine, and cases with associated exercise-induced movement disorders.

Prior to this study, a GLUT1DS family with PED and IGEs had already been described.[37] This family showed onset of epilepsy in adolescence/childhood but, oddly and atypically, clear and definite EEG focus. Tzadok et al.[27] recently reported a series of eight patients with supposed IGEs but quite atypical features, namely: absence epilepsy without myoclonias but with 3/sec spike-and-wave discharges interspersed with polyspike waves, myoclonic absences associated with ataxia and mild mental retardation, and aspecific seizures with PED. A quarter of these patients with epilepsy were found to have IGEs and the authors showed GLUT1 deficiency to be an important cause of IGEs.

At present, GLUT1 deficiency should be considered the most common known monogenic cause of atypical IGEs, and this raises the question of whether abnormalities in glucose delivery form part of a general, shared mechanism in IGEs.

GLUT1 deficiency syndrome should not really be regarded as a clinical feature of known epileptic syndromes (myoclonus-astatic epilepsy, absences epilepsy, etc.); rather GLUT1DS is a broad, complex syndrome that includes seizures with specific semiology possibly linked to known epileptic syndromes.

3.2.4. Movement disorders

Subjects with GLUT1DS commonly present complex movement disorders, which can be characterized by ataxia, dystonia, and chorea. These disorders can be continuous and/or paroxysmal and can fluctuate in response to different environmental stressors.[8] The most frequent stressors are fasting, infections, prolonged exercise, and anxiety or other emotions. Pons et al.[38] listed the most frequent movement disorders in 57 GLUT1DS patients: gait disturbances such as ataxia with/without spasticity (89%), action limb dystonia (86%), chorea (75%), cerebellar action tremor (70%), non-epileptic paroxysmal events (28%), dyspraxia (21%), and myoclonus (16%).

Epilepsy and movement disorders can occur either separately or in combination.[39] Severe motor disorders, including dyskinesia, ataxia, chorea and spasticity, associated with severe mental retardation, have been observed in the absence of seizures.[17]

Paroxysmal choreoathetosis with spasticity, previously known as dystonia type 9 (DYT9), and PED, previously known as dystonia type 18 (DYT18), are now recognized to be part of the phenotypic spectrum of GLUT1DS.[14,22,23]

Other paroxysmal events that can be observed include weakness, lethargy, somnolence, sleep disturbances, migraines,[23] writer's cramp, parkinsonism, dyspraxia, and non-kinesigenic dyskinesia.[15,40]

3.2.5. Hemolytic anemia

GLUT1 is the primary mediator of glucose transport across the endothelium of the blood–brain barrier, into and out of astrocytes, and into erythrocytes. However, there are rare reports of a correlation between anemia and GLUT1: Weber et al.,[23] identified a mutation (Q282_S285del) in the pore region of GLUT1 in a family with PED and hemolytic anemia; functional studies were performed in erythrocytes, and the mutation was found to explain the observed permanent cation leak responsible for the hemolytic anemia in this family.

Flatt et al.[41] suggested that two cases of stomatin-deficient cryohydrocytosis (a rare form of stomatocytosis) associated with a cold-induced cation leak, hemolytic anemia, hepatosplenomegaly, cataracts, seizures, mental retardation, and movement disorder, previously reported by them, were associated with the SLC2A1 mutation Gly286Asp.

Given the rarity of such descriptions we can affirm that haploinsufficiency of GLUT1 is not always associated with hemolytic anemia; this outcome depends on the type of GLUT1 mutation and whether this leads to cation leakage via the erythrocyte membrane.[42]

Another extra-neurological sign we have frequently observed in our GLUT1DS cases is prognathism: this could be a gestalt sign worth remembering.

4. Diagnosis

4.1. Lumbar puncture

The distinctive biomarker for GLUT1DS is low CSF glucose concentration, or hypoglycorrhachia.[12]

Table 1

Year	Glucose				Clinic			
	Article	Total patients	CSF mg/dl	Blood/CSF ratio	MR	Seizure	Motor signs	Other
2003	Leary et al.	20	<40	NA	+	GTC, Ab, FS, MS, AS	–	–
2005	Klepper et al.	15	32	0.39	+	+	At, Dy	–
2006	Friedman et al.	1	35	0.40	+	FS	PED, Dy, Cho, Ps	–
2007	Klepper and Leiendecker	84	31	0.35	–	+	H, At, Dy, PED, Ps	–
2008	Weber et al.	4	NA	0.39–0.55	+	+	PED	Ha
2008	Suls et al.	25	NA	NA	+/–	Ab, GTV, FS, MS	PED, Cho, Dy	–
2008	Zorzi et al.	3	26–31	0.33–0.38	+	+	PED, Dy, Dys, AT Ps	–
2009	Klepper et al.	2	36	0.44	?	?	?	?
2010	Leen et al.	54	31–34	0.36–0.41	+	+	At, Dy, Cho, Ps	–
2010	Mullen et al.	15	NA	NA	+/–	Ab, FS, MAS	PED	–
2009	Suls et al.	4	NA	NA	–	Ab, GTC, MS	PED	–
2010	Suls et al.	15	<40	NA	Classical phenotipe			
			40–50	NA	Milder phenotipe			
2010	Urbizu et al.	2	NA	0.37–0.4	–	Ab, MS	PED	Wc
2011	Anheim et al.	1	40	0.50	+	–	At, PED	W
2011	Byrne et al.	2	36	0.42––0.44	–	rS Ab	PED, At, Cho	W
2011	Fujii et al.	3	31–38	0.40–0.41	+	GTC	PED, At, Dys, Ps	W
2011	Fung et al.	2	32–34	0.38	+	MS, AA	At, Dy	W
2011	Gobken et al.	9	NA	0.26–0.43	+/–	FS, Ab, MS	Dy, At, Ps, PED	–
2011	Koy et al.	1	34	0.42	+	GTC	PED	W
2011	Hashimoto et al.	12	NA	0.28–0.48	+	GTC PS AS Ab TS	At, Dy	–
2011	Ito et al.	6	NA	0.30–0.45	+	AS, AA, MS, FS, Ab	At, Dys, Ps, Dy	W
2011	Mullen et al.	4	32–37	0.42	+/–	MAS	Tr, Dys, AT, PED	–
2011	Yang et al.	71	32.31 + –4.1	0.37 + –0.08	NA	NA	NA	NA
			35.53 + –5.83	0.38 + –0.07	NA	NA	NA	NA
2012	Afawi et al.	5	NA	NA	–	GTC	PED	–
2012	Arsov et al.	7	38–49	<0.48	–	MS, Ab, GTC	PED	–
2012	Gagliardi et al.	4	NA	NA	+	+	Cho, PED	–
2012	Gramer et al.	2	38–40	0.41	+	MAS, GTC, AS	At, PED, Dy, Dys	–
2012	kitamura et al.	1	26	0.3	–	Ab	At, PED	W
2012	Pong et al.	57	NA	NA	+	Ab GTC, CFS, MS, TS, SFS, Sp	NA	NA
2012	Spatola et al.	NA	45	0.19–0.5	+	+	PED, H, At	W
2012	Vieker et al.	1	34	0.39	–	MS, Ab, GTC	–	–
2013	Tzadok et al.	8	30–49	0.39–0.54	+/–	GTC, MS, AA, Ab	At, PED	–

rS: refractory seizures; FS: focal seizures; Ab: absences; AA: atipical absences; MS: myoclonic; MAS myoclonic-astatic seizures; AS: atonic seizure, GTC: Generalized Tonic Clonic; TS Tonic Seizure. MR: mental retardation. H: Hypotonia; At: ataxia; Dys: dysarthia; Dy: dystonia; Cho: chorea, Ps: piramidal signs, Tr: tremor. W: weakness, M: migraine; Wc: Writer's cramp; Ha: Hemolytic Anemia.

Hypoglycorrhachia can also be found in other neurological conditions, such as prolonged seizures/status epilepticus, mitochondrial diseases, infectious meningitis, hypoglycemic states, subarachnoid hemorrhage, and meningeal carcinomatosis.[43,44] If these conditions are ruled out, the presence of hypoglycorrhachia strongly indicates GLUT1DS.

The CSF-to-blood glucose ratio is superior to the absolute glucose level in CSF. Normal CSF-to-blood glucose ratios are above 0.6.

Initially, a CSF-to-blood glucose ratio of 0.33–0.37 (CSF concentration 40 mg/dl)[18] was set as the cut-off value for a diagnosis of GLUT1DS in suspected cases. However, with the increasing recognition of milder allelic variants, higher values are now being applied (see Table 1).

However, this aspect continues to be debated in the literature; Suls et al.,[22,34] Mullen et al.,[31] Weber et al.[23] and our own experience suggest that milder phenotypes, especially ones characterized by movement disorders without epilepsy, can be associated with ratios of up to 0.59 (CSF glucose 60 mg/dl), even though, as affirmed by De Vivo and Wang[45] and Yang et al.,[13] in the vast majority of cases (>90%) values are lower than 0.37. Several attempts have been made to correlate clinical severity with the degree of hypoglycorrhachia,[8] but conclusive results are still lacking.

These observations indicate that the normal range for CSF glucose has never been defined properly. The risk that some patients with normal glycorrhachia might even go undiagnosed and untreated suggests that molecular analysis of the SLC2A1 gene should be used as an alternative gold standard for diagnosing GLUT1DS, when the condition is strongly suspected.[29]

On the other hand, Klepper and Leiendecker reported that about 30% of patients in their cohort of 84 patients with hypoglycorrhachia[5] did not carry mutations, which suggests the existence of alternative disease mechanisms. In these patients with highly suggestive clinical findings and low CSF glucose, treatment with KD should always be attempted.

Lumbar puncture should be performed in the fasting state, and the blood sample used for measurement of glucose concentration should be obtained immediately before the lumbar puncture to avoid stress-related hyperglycemia.

Reduced lactate concentration (below 1.4 mmol/l)[19,20] could be another CSF marker of GLUT1DS, although in our personal experience we have not found lactate levels in GLUT1DS to be significantly lower than normal (mean value 1.6 mmol/l). Klepper[29] recently affirmed that CSF lactate is never elevated in GLUT1DS.

4.2. Erythrocyte 3-OMG uptake

As the GLUT1 gene is also expressed in erythrocytes, the finding of decreased uptake of 3-O-methylglucose (3-OMG) into erythrocytes could also serve to confirm a diagnosis of GLUT1DS.

Pathogenic mutations cause haploinsufficiency, and therefore decrease 3-OMG uptake by approximately 50%.[19] However, the phenotype associated with the T295M mutation in SLC2A1 shows normal 3-OMG uptake in erythrocytes, and thus leads to

false-negative results in patients carrying pathogenic mutations.[20] Furthermore, these investigations are not commercially available and are demanding in terms of protocol, time, sample size and sample quality.[29]

4.3. Molecular analysis

Approximately 70–80% of patients carry SLC2A1 mutations.[15] Genetic testing is commercially available worldwide. It should include polymerase chain reaction (PCR) sequencing of all 10 exons, splice site, and the promoter region.[7] If it is negative, deletions/duplications within the SCL2A1 gene can be detected by multiplex ligation-dependent probe amplification (MLPA).[8]

In SCL2A1-negative patients, GLUT1DS can be diagnosed only in the presence of clear hypoglycorrhachia. In such cases it is, indeed, reasonable to suspect GLUT1DS and to initiate KD treatment. An immediate response to the diet will support the diagnosis.[29]

These patients constitute a particularly interesting subset as they might carry defects in GLUT1 assembly, three-dimensional GLUT1 folding, GLUT1 trafficking to the cell, or GLUT1 activation.[5]

5. EEG findings

No characteristic electroencephalography (EEG) pattern in GLUT1DS has yet been identified, and patients can actually show a normal interictal EEG.[6,30]

Infants with GLUT1DS can present with multifocal spike discharges on EEG, underlying infantile focal seizures (non-generalized) that may include eye movements, cyanotic spells, etc.[46] Subsequently, as the brain matures, these seizures become synchronized and clinically manifest themselves as generalized events associated with 3–4 Hz spike-and-wave discharges.

Tzadoket al.[27] maintain that the presence of polyspike wave discharges in the context of absence epilepsy without myoclonus or prominent aggravation of generalized polyspike wave discharges during sleep – which they did not usually observe in IGE patients – could be characteristic signs.

However, on the basis of our personal experience, we suggest that the above-mentioned features can also be present in "simple" forms of IGE. In our sample of GLUT1DS patients (article in press), we found that many "unusual" signs can be detected in idiopathic forms, such as the presence of atypical spike-and-wave discharges. In our view, these findings cannot be taken as characteristic signs.

On the contrary, some authors have reported improvement in the EEG findings post-prandially or after intravenous administration of glucose.[47] These EEG recordings could offer a simple screening test for GLUT1DS, even though, on their own, they cannot be considered diagnostic.

Marin-Valencia et al.[48] recently demonstrated in a mouse model of GLUT1DS that thalamocortical hypersynchronization is an important mechanism in GLUT1DS epileptogenesis due to impaired glucose uptake. Intrinsic cortical hyperexcitability arises from failure of internal thalamic inhibition, which causes propagation of excitation to the cortex; this could explain the frequent clinical presentation of absence epilepsy in patients with GLUT1DS. Moreover, because brain cells derive most of their energy from glucose, GLUT1 deficiency also impairs the synthesis of key molecules involved in energy production and neurotransmission, such as acetyl-CoA, tricarboxylic acid cycle intermediates and other derivatives.

6. Brain imaging

Neuroimaging findings in patients with GLUT1DS are not significant. Magnetic resonance imaging (MRI) scans of patients with GLUT1DS mostly show either normal findings[6] or occasionally mild enlargement of inner and outer CSF spaces.[5,49]

Cerebral fluorodeoxyglucose positron emission tomography (PET) in 14 patients with the classical GLUT1DS phenotype revealed a global decrease in glucose uptake in the cortex, more severe in the mesial temporal regions and thalami, and less marked in the basal ganglia.[22] The distinctive PET signature appears in early infancy and persists into adulthood regardless of disease severity or KD therapy. Although PET is readily available in clinical practice, the sensitivity and specificity of PET in the diagnosis of GLUT1DS have not yet been established.[50]

7. Treatments

7.1. Ketogenic diet

In the fasting state, brain glycogen storage is exhausted within minutes. The brain cannot utilize amino acids and fat to produce energy and, in the absence of glycogen, switches to ketones as an alternative fuel to maintain function. Ketones are generated in the liver from fatty acid degradation and enter the brain via facilitated diffusion mediated by the monocarboxylate transporter 1 (MCT1 transporter). This mechanism is particularly effective in infants and young children in whom ketone extraction and utilization is three-to-four-fold higher than in adults.[2]

The KD is a high-fat, carbohydrate-restricted diet that mimics the metabolic state of fasting. It has been used safely and effectively for decades in intractable childhood epilepsy.[1] The classic KD, as developed by the Johns Hopkins University, uses long-chain triglycerides and consists of 4 g of fat to every 1 g of carbohydrate and protein combined (4:1 ratio) with supplemental vitamins and minerals. The spectrum of the KD has now increased considerably[51] and includes several alternative diets such as the classic KD with a 3:1 ratio, medium-chain triglycerides (MCTs), the modified Atkins diet (MAD) (which provides 10 g carbohydrates/day in children and 15 g/day in adults), and the low glycemic index treatment (LGIT), which restricts the consumption of certain types of carbohydrate-containing foods.

Novel indications for KD include disorders of brain energy metabolism such as pyruvate dehydrogenase deficiency (PDHP) and GLUT1DS.[52]

Although, in epilepsy, the mechanism of action underlying the effectiveness of the KD is not yet clear,[53] in GLUT1DS it essentially provides an alternative fuel source. The effectiveness of the KD in GLUT1DS might be enhanced by its anticonvulsant action. The vast majority of GLUT1DS patients obtain seizure freedom with the classical 4:1 or 3:1 formula, allowing anticonvulsant therapy to be withdrawn.[5] There are a few reports in which the KD was not fully effective and anticonvulsants were not completely eliminated.[54,55]

The KD also has a positive effect on movement disorders such as hypotonia, ataxia, dystonia, and PED.[24,56]

The impact of KD treatment on developmental delay appears less prominent.[6] However, several authors have reported a marked increase in alertness and activity in patients on the KD.

Our own experience has shown that introduction of the KD in the first years of life in patients with GLUT1DS guarantees a better cognitive outcome. The literature contains numerous reports of improved psychomotor impairment, but these are hard to verify in case–control studies.

As the developing brain in the young child requires more energy, the KD should be started as early as possible whenever GLUT1DS is suspected. There are also reports of voluntary intake of large amounts of fat-containing food in patients subsequently diagnosed as GLUT1DS.[57]

It remains unclear whether a rigorous KD is essential in GLUT1DS. Seizure and movement disorder control can be achieved

by a 2:1 or 3:1 ketogenic ratio but the relationship between ketosis and neurodevelopmental outcome remains undetermined. The MAD is also well tolerated and provides effective symptom control; furthermore, this diet has the advantage of being easy to prepare and more palatable, which are important requirements for good compliance. On the contrary there are no data about the LGIT in GLT1DS and studies are needed to investigate the possible effectiveness of this treatment. Finally, we have little direct experience of MCT therapy and therefore cannot express an opinion on this option. We feel that MCTs could be integrated into

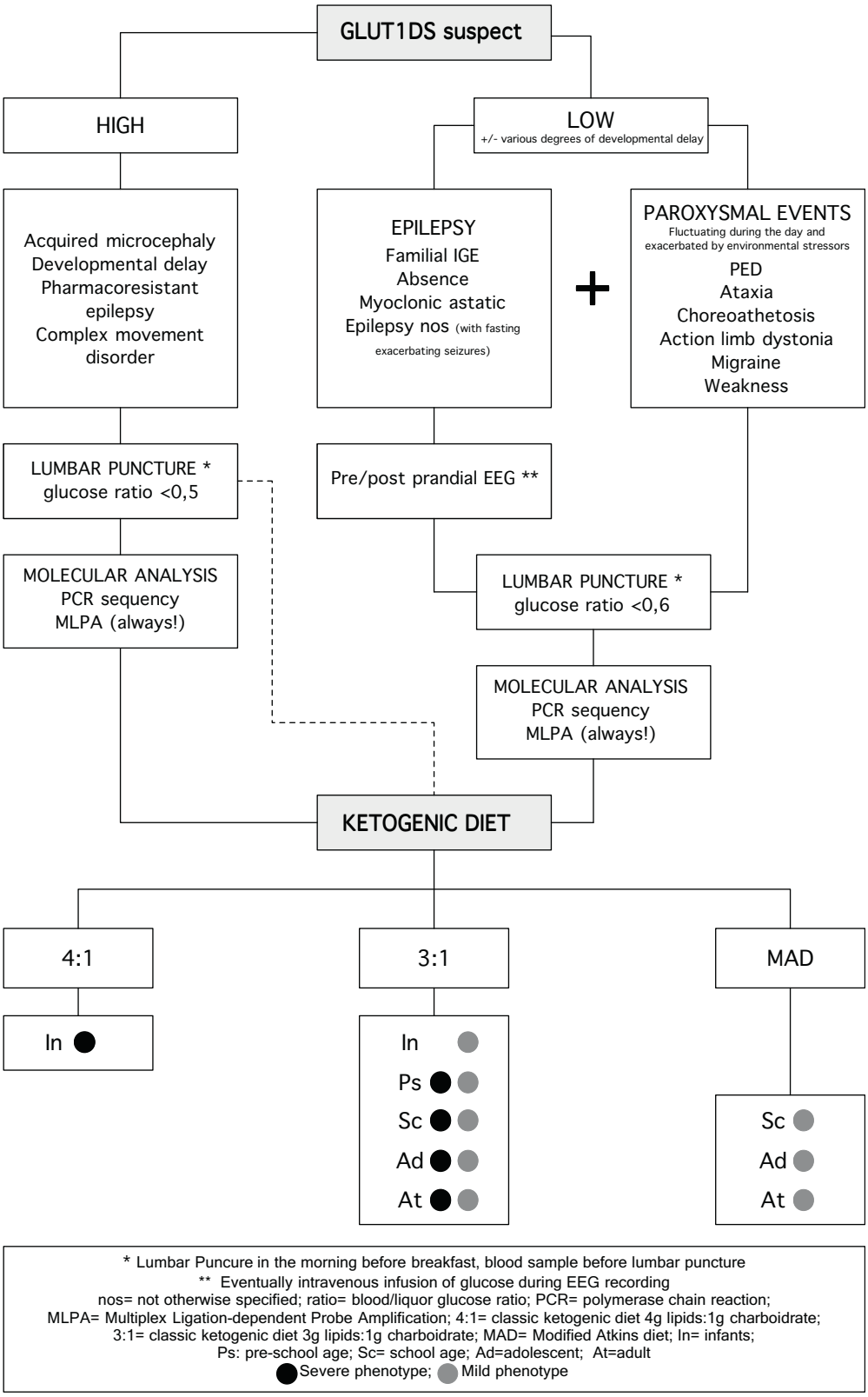

Fig. 1.

the above diets to make them more manageable, however it is not our practice to use only MCTs in our drug-resistant epilepsy or GLUT1DS patients.

Fig. 1 details, in addition to the diagnostic procedure, our clinical practice as regards the use of the KD in GLUT1DS patients at different ages and in different classes of severity.

There remain various challenges to be addressed. These include determination of the most efficient ratio and composition of the diets, and the development of treatment strategies in GLUT1DS adults.

The KD approach has advanced considerably over the past years, to the point that it is now considered a first-line therapy in infantile spasms, MAE, Dravet syndrome, and status epilepticus [including febrile infection-related epilepsy syndrome]. KDs are also now being increasingly studied for neurological conditions other than epilepsy, including Alzheimer's disease and cancer.[53] Further research could shed light on the mechanisms that may make metabolism-based therapy particularly helpful in terms of anticonvulsant and possibly neuroprotective effects.

7.2. Additional measures

Treatment with a KD should be complemented by additional measures: pharmacological agents known to impair GLUT1 function, e.g. caffeine, phenobarbital, diazepam, chloral hydrate and tricyclic antidepressants, should be avoided.[49]

There are also reports of the use of alternative compounds for the treatment of GLUT1DS.

Alpha lipoic acid is an antioxidant that serves as a co-enzyme in energy metabolism. It neutralizes free radicals, improves cellular glucose uptake by stimulating the insulin signal cascade, reduces inflammation, and binds with metals. Alpha lipoic acid supplementation has been recommended in GLUT1DS on the basis of the observation that it improves glucose transport in cultured muscle cells via mobilization of the GLUT4 transporter from intracellular pools;[20,30] however, to date there are no published data in humans to demonstrate its effectiveness.

Acetazolamide was reported to be beneficial for paroxysmal dyskinesias in a single patient with GLUT1DS.[58]

Triheptanoin is a triglyceride that has been used as an anaplerotic substrate in humans to treat inherited metabolic diseases such as pyruvate carboxylase deficiency and carnitine palmitoiyltransferase II deficiency.[59] It is metabolized into five carbon compounds that easily cross the blood–brain barrier via monocarboxylate transporters and may enhance the effect of the regular ketones as an alternative fuel for the brain. Although promising in theory, there are currently no clinical data to support the use of this compound in GLUT1DS.

8. Follow-up and outcome

Regular follow-up visits are needed after a diagnosis of GLUT1DS in order to monitor the patient's clinical evolution.

Patients starting KD treatment should be monitored particularly closely.

In accordance with the 2011 Italian consensus statement on KD therapy,[39] we recommend that follow-up of GLUT1DS children/adults include regular dietary and neurological evaluations and EEG, performed at least five times in the first year of treatment (after 1, 3, 6, 9, and 12 months). Annual cognitive and developmental assessments are also recommended, as are regular blood and metabolic evaluations.

In contrast to intractable childhood epilepsy patients, individuals affected by GLUT1DS should continue the diet into adolescence to meet the increased energy demands of the developing brain.[52] In our opinion, KD treatment can be useful in adulthood, too, because even though epilepsy seems to disappear in adulthood, the movement disorder can persist unchanged and there are, as yet, no reliable data confirming a stable cognitive outcome in adult patients with GLUT1DS. More important, the KD might exert neuroprotective effects. Low glucose concentrations in the CSF can lead to oxidative DNA damage and lipid peroxidation. Chronic ketosis limits the generation of reactive oxygen species and boosts energy reserve capacity, which is important in sustaining the electrophysiological activities essential for performing brain function.[60] Furthermore, in GLUT1DS patients, KD therapy could be beneficial to organs expressing GLUT1 at high levels such as the retina, colon, ovaries and testicles.[1]

For these reasons, if there are no serious side effects, we recommend lifelong KD treatment in GLUT1DS patients, even if symptom control is not complete. It is necessary to compensate for the deficit caused by the failure of glucose to cross the blood–brain barrier in order to reduce the long-term risks associated with the disease.

In our experience, compliance is much better in GLUT1DS than in the other conditions for which KD treatment is indicated. According to the literature there is a good level of satisfaction: up to 75% of patients consider the diet effective and 50% tolerate and accept it.[55]

The question of when to discontinue AEDs in patients with GLUT1DS is not really debated in the literature. According to our protocol, if seizures and non-epileptic paroxysmal events have disappeared, gradual reduction of AEDs can start from the first year after the introduction of the KD. If the diet does not completely control the symptoms, AEDs are continued at the most effective and best tolerated dose.

No information is available on the long-term efficacy and tolerability of the treatment in GLUT1DS patients, but non-GLUT1DS seizure-free epileptic patients on the diet for >10 years have been reported.[61]

9. Conclusions

GLUT1 deficiency syndrome results from impaired glucose transport into the brain. Recently the clinical spectrum of GLUT1DS has been broadened and it is becoming less meaningful to consider the disease in terms of "classical" and "non-classical" phenotypes.

On the basis of current knowledge, this disease should be suspected (Fig. 1) and a CSF investigation (with determination of the CSF-to-blood glucose ratio) strongly recommended in the presence of:

- any seizures that are refractory and/or influenced by fasting, especially if associated with mild neurological (pyramidal or extra-pyramidal) signs and/or mental impairment and/or atypical EEG features and/or a family history of epilepsy or movement disorder.
- any history of unexplained paroxysmal events – especially if PED – associated with previous self-limited seizures and/or mental impairment and/or a family history of epilepsy or movement disorder.

Other signs such as microcephaly, mental retardation, and dysarthria are frequently observed in GLUT1DS patients, however our experience shows that they are not hallmarks.

An extra-neurological sign we frequently observed in our GLUT1DS cases was prognathism: this could be a gestalt sign worth remembering.

The question of whether or not to perform lumbar puncture has been extensively debated in the literature. Even today, most patients presenting with epilepsy or a movement disorder do not have a diagnostic lumbar puncture.

In accordance with De Vivo and Wang,[45] we emphasize the continuing value of the lumbar puncture as the classical approach to the neurological patient with an unexplained condition. This procedure has withstood the test of time and remains cost-efficient. It is true that gene sequencing is an increasingly available, non-invasive test with a pretest probability of 1% for IGEs,[36] rising to 10% for early-onset absence epilepsy.[31] However, we do not consider it useful to perform mutational analysis of the SLC2A1 gene in all patients with early-onset absence epilepsies or epilepsy with myoclonic-atonic seizures,[62] believing, instead, that the analysis should be reserved for patients with highly suggestive clinical findings and low CSF glucose or borderline clinical findings and CSF glucose who require genetic testing to confirm the diagnosis prior to starting a KD. This approach is certainly less expensive than wider genetic screening, and also feasible worldwide.

At present, it seems most interesting to focus on those patients who have a clinical picture highly suggestive of GLUT1DS, a low glycorrhachia value, and possibly a good response to the KD, but who are negative on gene SLC2A1 sequencing and MLPA. In these *SLC2A1*-negative GLUT1DS patients other potential disease mechanisms could be at work.[63]

This is why sequencing of the entire exome should be performed in an attempt to identify other genes possibly implicated in GLUT1 protein assembly, three-dimensional folding, trafficking to the cell, or activation.

It is essential diagnose this entity as early as possible to allow prompt compensation, through the KD, for the brain's lack of fuel. Early identification of children with GLUT1DS is important in order to avoid submitting them to possibly ineffective or potentially detrimental treatments with anticonvulsants, and to ensure that their brains are provided with an alternative energy source during a time of increased cerebral metabolism.

On the basis of current knowledge, it is not possible to say with absolute certainty that the condition of GLUT1DS patients never deteriorates. The hallmark deficiency of glucose in the CNS, if allowed to persist for many years, could be responsible for brain atrophy, which could be observed on the MRI scans of these patients, and for a moderate but steady reduction of IQ, as well as for the maintenance of more or less drug-resistant epilepsy and a disabling movement disorder. The few GLUT1DS adult patients identified to date do not provide sufficient evidence to clarify our doubts in this regard.

Ongoing research to discover pathogenic mechanisms underlying different phenotypes, the availability of new animal models of GLUT1DS, growing patient numbers, and the diffusion of knowledge of this relatively "new" disease could help us to provide answers to some of the many still open questions about GLUT1DS. Moreover exomewide sequencing in a small number of patients with a similar phenotype could disclose other genes implicated in GLUT1DS.

Ethical approval

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest statement

None of the authors has any conflict of interest to disclose

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References

1. Klepper J. Glucose transporter deficiency syndrome (GLUT1DS) and the ketogenic diet. *Epilepsia* 2008;**49**(Suppl 8):46–9.
2. Cremer JE. Substrate utilization and brain development. *Journal of Cerebral Blood Flow and Metabolism* 1982;**2**:394–407.
3. Vannucci SJ, Maher F, Simpson IA. Glucose transporter proteins in brain: delivery of glucose to neurons and glia. *Glia* 1997;**21**(September (1)):2–21.
4. Klepper J, Voit T. Facilitated glucose transporter protein type 1 (GLUT1) deficiency syndrome: impaired glucose transport into the brain – a review. *European Journal of Pediatrics* 2002;**161**:295–304.
5. Klepper J, Leiendecker B. GLUT1 deficiency syndrome – 2007 update. *Developmental Medicine and Child Neurology* 2007;**49**:707–16.
6. Brockmann K. The expanding phenotype of GLUT1-deficiency syndrome. *Brain and Development* 2009;**31**:545–52.
7. Schneider SA, Paisan-Ruiz C, Garcia-Gorostiaga I, Quinn NP, Weber YG, Lerche H, et al. GLUT1 gene mutations cause sporadic paroxysmal exercise-induced dyskinesias. *Movement Disorders* 2009;**24**:1684–8.
8. Leen WG, Klepper J, Verbeek MM, Leferink M, Hofste T, van Engelen BG, et al. Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. *Brain* 2010;**133**:655–70.
9. Graham Jr JM. GLUT1 deficiency syndrome as a cause of encephalopathy that includes cognitive disability, treatment-resistant infantile epilepsy and a complex movement disorder. *European Journal of Medical Genetics* 2012;**55**:332–4.
10. Mueckler M, Caruso C, Baldwin SA, Panico M, Blench I, Morris HR, et al. Sequence and structure of a human glucose transporter. *Science* 1985;**229**:291–5.
11. Salas-Burgos A, Iserovich P, Zuniga F, Vera JC, Fischbarg J. Predicting the three dimensional structure of the human facilitative glucose transporter glut1 by a novel evolutionary homology strategy: insights on the molecular mechanism of substrate migration, and binding sites of glucose and inhibitory molecules. *Biophysical Journal* 2004;**87**:2990–9.
12. Rostein M, Englestad K, Yang H, Wang D, Levy B, Chung WK, et al. Glut1 deficiency: inheritance pattern determined by haploinsufficiency. *Annals of Neurology* 2010;**68**(6):55–8.
13. Yang H, Wang D, Engelstad K, Bagay L, Wei Y, Rotstein M, et al. Glut1 deficiency syndrome and erythrocyte glucose uptake assay. *Annals of Neurology* 2011;**70**(6):96–1005.
14. Klepper J, Sheffer H, Elsaid MF, Kamsteeg EJ, Leferink M, Ben-Omran T. Autosomal recessive inheritance of GLUT1 deficiency syndrome. *Neuropediatrics* 2009;**40**(5):207–10.
15. Pérez-Dueñas B, Prior C, Ma Q, Fernández-Alvarez E, Setoain X, Artuch R, et al. Childhood chorea with cerebral hypotrophy: a treatable GLUT1 energy failure syndrome. *Archives of Neurology* 2009;**66**(11):410–4.
16. Nickels K, Wirrell E. GLUT1-ous maximus epilepticus: the expanding phenotype of GLUT1- mutations and epilepsy. *Neurology* 2010;**75**(5):390–1.
17. Verrotti A, D'Egidio C, Agostinelli S, Gobbi G. GLT1 deficiency: when to suspect and how to diagnose? *European Journal of Paediatric Neurology* 2012;**16**:3–9.
18. Aktas D, Utine EG, Mrasek K, Weise A, von Eggeling F, Yalaz K, et al. Derivative chromosome 1 and GLUT1 deficiency syndrome in a sibiling pair. *Molecular Cytogenetics* 2010;**3**(1):10.
19. De Vivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Harik SI. Defective glucose transport across the blood–brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. *The New England Journal of Medicine* 1991;**325**(10):703–9.
20. De Vivo DC, Leary L, Wang D. Glucose transporter 1 deficiency syndrome and other glycolytic defects. *Journal of Child Neurology* 2002;**17**(Suppl 3. 3S15–3S23.
21. Zorzi G, Castellotti B, Zibordi F, Gellera C, Nardocci N. Paroxysmal movement disorders in GLUT1 deficiency syndrome. *Neurology* 2008;**71**(2):46–148.
22. Suls A, Dedeken P, Goffin K, Van Esch H, Dupont P, Cassiman D, et al. Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in SLC2A1, encoding the glucose transporter GLUT1. *Brain* 2008;**131**(Pt7):831–44.
23. Weber YG, Storch A, Wuttke TV, Brockmann K, Kempfle J, Nakjevic S. GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesia and induce haemolytic anemia by a cation leak. *Journal of Clinical Investigation* 2008;**118**(6):2157–68.
24. Friedman JR, Thiele EA, Wang D, Levine KB, Cloherty EK, Pfeifer HH. Atypical GLUT1 deficiency with prominent movement disorder responsive to ketogenic diet. *Movement Disorders* 2006;**21**(2):241–5.
25. Rostein M, Doran J, Yang H, Ullner PM, Engelstad K, De Vivo DC. Glut1 deficiency and alternating hemiplegia of childhood. *Neurology* 2009;**73**(23):2042–4.
26. Urbizu A, Cuenca-León E, Raspall-Chaure M, Gratacòs M, Conill J, Redecillas S, et al. Paroxysmal exercise-induced dyskinesia, writer's cramp, migraine with aura and absence epilepsy in twin brothers with a novel SLC2A1 missense mutation. *Journal of Neurological Sciences* 2010;**15/295**(1–2):110–3.
27. Tzadok M, Nissenkorn A, Porper K, Matot I, Marcu S, Anikster Y, et al. The many faces of Glut1 deficiency syndrome. *Journal of Child Neurology* 2013. Published online 2013, January 22.
28. Klepper J, Wang D, Hinton VJ, Nordly Jr DR, ODK R, De Vivo DC. Glucose transporter protein syndrome (GPTS). *Neuropediatrics* 1998;(29):A9.
29. Klepper J. GLUT1 deficiency syndrome in clinical practice. *Epilepsy Research* 2012;**100**:272–7.
30. Pong AW, Geary BR, Engelstad KM, Natarajan A, Yang H, De Vivo DC. Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcome. *Epilepsia* 2012;**53**(9):503–10.

31. Mullen SA, Suls A, De Jonghe P, Berkovic SF, Scheffer IE. Absence epilepsies with widely variable onset are a key feature of familial GLUT1 deficiency. *Neurology* 2010;**75**(5):432–40.
32. Vieker S, Schmitt J, Langer A, Schmidt W, Klepper J. Unusual sensitivity to steroid treatment in intractable childhood epilepsy suggests GLUT1 deficiency syndrome. *Neuropediatrics* 2012;**43**(5):75–8.
33. Mullen SA, Marini C, Suls A, Mei D, Della Giustina E, Buti D, et al. Glucose transporter 1 deficiency as a treatable cause of myoclonic astatic epilepsy. *Archives of Neurology* 2011;**68**(9):1152–5.
34. Suls A, Mullen SA, Weber YG, Verhaert K, Ceulemans B, Guerrini R, et al. Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. *Annals of Neurology* 2009;**66**(3):15–9.
35. Gökben S, Yilmaz S, Klepper J, Serdaroğlu G, Tekgül H. Video/EEG recording of myoclonic absence in GLUT1 deficiency syndrome with a hot-spot R126C mutation in the SLC2A1 gene. *Epilepsy Behavior* 2011;**21**(2):2000–2.
36. Arsov T, Mullen SA, Rogers S, Phillips AM, Lawrence KM, Damiano JA, et al. Glucose transporter 1 deficiency in the idiopathic generalized epilepsies. *Annals of Neurology* 2012;**72**(5):807–15.
37. Afawi Z, Suls A, Ekstein D, Kivity S, Neufeld MY, Oliver K, et al. Mild adolescent/adult onset epilepsy and paroxysmal exercise-induced dyskinesia due to GLUT1 deficiency. *Epilepsia* 2010;**51**(12):466–9.
38. Pons R, Collins A, Rotstein M, Engelstad K, De Vivo DC. The spectrum of movement disorders in Glut-1 deficiency. *Movement Disorder* 2010;**15/25**(3):275–81.
39. Veggiotti P, Burlina A, Coppola G, Cusmai R, De Giorgis V, Guerrini R, et al. The ketogenic diet for Dravet syndrome and other epileptic encephalopathies: an Italian consensus. *Epilepsia* 2011;**52**(Suppl 2):83–9.
40. Overweg-Plandsoen WC, Groener JE, Wang D, Onkenhout W, Brouwer OF, Bakker HD, et al. GLUT-1 deficiency without epilepsy – an exceptional case. *Journal of Inherited Metabolic Disease* 2003;**26**(6):59–63.
41. Flatt JF, Guizouarn H, Burton NM, Borgese F, Tomlinson RJ, Forsyth RJ, et al. Stomatin-deficient cryohydrocytosis results from mutations in SLC2A1: a novel form of GLUT1 deficiency syndrome. *Blood* 2011;**10/118**(19):5267–77.
42. Bawazir WM, Gevers EF, Flatt JF, Ang AL, Jacobs B, Oren C, et al. An infant with pseudohyperkalemia, hemolysis, and seizures: cation-leaky GLUT1-deficiency syndrome due to a SLC2A1 mutation. *The Journal of Clinical and Endocrinology Metabolism* 2012;**97**(June (6). E987-93.
43. Silver TS, Todd JK. Hypoglycorrhachia in pediatric patients. *Pediatrics* 1976;**58**(1):7–71.
44. Huang HR, Chen HL, Chu SM. Clinical spectrum of meningococcal infection in infants younger than six months of age. *Chang Gung Medical Journal* 2006;**9**(1):107–13.
45. De Vivo DC, Wang D. Glut1 deficiency: CSF glucose. How low is too low? *Revue Neurologique* 2008;**164**(11):877–80.
46. Leary LD, Wang D,Nordli Dr Jr, Engelstad K, De Vivo DC. Seizure characterization and electroencephalographic features in Glut-1 deficiency syndrome. *Epilepsia* 2003;**44**(May (5)):701–7.
47. von Moers A, Brockmann K, Wang D, Korenke CG, Huppke P, De Vivo DC, et al. EEG features of glut-1 deficiency syndrome. *Epilepsia* 2002;**43**(8):41–5.
48. Marin-Valencia I, Good LB, Ma Q, Duarte J, Bottiglieri T, Sinton CM, et al. Glut1 deficiency (G1D): epilepsy and metabolic dysfunction in a mouse model of the most common human phenotype. *Neurobiology of Disease* 2012;**48**(1):92–101.
49. Wang D, Pascual JM, Yang H, Englestad K, Mao X, Cheng J, et al. A mouse model for Glut-1 haploinsufficiency. *Human Molecular Genetics* 2006;**15**:1169–79.
50. Pascual JM, Van Heertum RL, Wang D, Englestad K, De Vivo DC. Imaging the metabolic footprint of Glut1 deficiency on the brain. *Annals of Neurology* 2002;**52**(4):458–64.
51. Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. *Epilepsia* 2009;**50**(2):304–17.
52. Veggiotti P, Teutonico F, Alfei E, Nardocci N, Zorzi G, Tagliabue A, et al. Glucose transporter type 1 deficiency: ketogenic diet in three patients with atypical phenotype. *Brain and Development* 2010;**32**(5):404–8.
53. Kossoff EH, Hartman AL. Ketogenic diets: new advances for metabolism-based therapies. *Current Opinion in Neurology* 2012;**25**(2):73–8.
54. Freeman JM, Kossoff EH, Hartman AL. The ketogenic diet: one decade later. *Pediatrics* 2007;**119**(3):35–43.
55. Coman DJ, Sinclair KG, Burke CJ, Appleton DB, Pelekanos JT, O'Neil CM, et al. Seizures, ataxia, developmental delay and the general paediatrician: glucose transporter 1 deficiency syndrome. *Journal of Paediatrics and Child Health* 2006;**42**(5):63–7.
56. Gramer G, Wolf NI, Vater D, Bast T, Santer R, Kamsteeg EJ, et al. Glucose transporter-1 (GLUT1) deficiency syndrome: diagnosis and treatment in late childhood. *Neuropediatrics* 2012;**43**(3):68–71.
57. Ito S, Oguni H, Ito Y, Ishigaki K, Ohinata J, Osawa M. Modified atkins diet therapy for a case with glucose transporter type 1 deficiency syndrome. *Brain and Development* 2008;**30**(3):26–8.
58. Koy A, Assmann B, Klepper J, Mayatepek E. Glucose transporter type 1 deficiency syndrome with carbohydrate-responsive symptoms but without epilepsy. *Developmental Medicine and Child Neurology* 2011;**53**(12):1154–6.
59. Klepper J, Fischbarg J, Vera JV, Wang D, De Vivo DC. GLUT1-deficiency: barbiturates potentiate haploinsufficiency in vitro. *Pediatric Research* 1999;**46**(6):77–83.
60. Anheim M, Maillart E, Vuillaumier-Barrot S, Flamand-Rouviére C, Pineau F, Ewenczyk C, et al. Excellent response to acetazolamide in a case of paroxysmal dyskinesias due to GLUT1-deficiency. *Journal of Neurology* 2011;**258**(2):316–7.
61. Groesbeck DK, Bluml RM, Kossoff EH. Long-term use of the ketogenic diet in the treatment of epilepsy. *Developmental Medicine and Child Neurology* 2006;**48**(12):78–81.
62. Scheffer IE. GLUT1 deficiency: a glut of epilepsy phenotypes. *Neurology* 2012;**78**:524–5.
63. Klepper J. Absence of SLC2A1 mutations does not exclude Glut1 deficiency syndrome. *Neuropediatrics* 2013. published online 2013, March 12.